clusion are primary immunodeficiency disorders, especially those associated with adenosine deaminase and nucleoside phosphorylase enzyme deficiency.

Not all children who are antibody-positive have clinical features of AIDS or laboratory abnormalities suggesting immunodeficiency. As the incubation period may exceed five years, these children should be followed carefully for the development of symptoms, immunodeficiency or both. Once the diagnosis is established, appropriate therapy may be instituted, including prophylactic trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia and intravenous administration of immune globulin to prevent both viral and bacterial infections.

A controversial area of pediatric AIDS relates to public health considerations. There is no evidence of casual spread of HTLV-III/LAV from infected persons to noninfected persons. Direct inoculation of the virus (blood transfusion) or sexual contact is required. Nevertheless, children with AIDS, or those who are antibody-positive but asymptomatic, have been ostracized and prevented from attending school. A physician caring for a child with AIDS may be deeply involved in educating parents, public health agencies, school boards and the public.

ARTHUR AMMANN, MD
South San Francisco, California

Ammann AJ: The acquired immunodeficiency syndrome in infants and children. Ann Intern Med 1985; 103:734-737

Oleske J, Minnefor A, Cooper R Jr, et al: Immune deficiency syndrome in children. JAMA 1983 May; 249:2345-2349

Rubinstein A, Sicklick M, Gupta A, et al: Acquired immunodeficiency with reversed T4/T8 ratios in infants born to promiscuous and drug addicted mothers. JAMA 1983 May; 249:2350-2356

Long-term Outcome in Infants With a Very Low Birth Weight

WITH THE ADVENT of highly specialized obstetric and neonatal management for high-risk mothers, fetuses and neonates, neonatal mortality has decreased sharply in the past two decades. The major contribution has been the increased survival in very-low-birth-weight infants (less than 1,501 grams). In the period 1950 to 1960, two thirds of the very-low-birth-weight infants died. An infant who weighed less than 1,001 grams at birth had less than a 5% chance of survival. On follow-up, more than half of the surviving very-low-birth-weight infants were found to have significant physical, neurologic and developmental handicaps.

Today many centers report survival rates of 80% in infants with birth weights of from 1,001 to 1,250 grams and 90% in infants weighing 1,251 to 1,500 grams. Are a greater number of very-low-birth-weight infants now surviving only to increase the number of handicapped persons in our society? Apparently not. The infants with birth weights of 1,001 to 1,500 grams, who represent more than 70% of the total very-low-birth-weight group, do well, with less than 10% showing major problems at preschool age. It would appear that perinatal and neonatal management today has proved successful in reducing both mortality and morbidity in infants who weigh more than 1,000 grams at birth.

On follow-up the problems that affected the larger very-low-birth-weight survivors born 25 years ago are now found in the very tiny infants with birth weights of less than 1,001 grams. Recent follow-up programs of infants born in the late 1970s and early 1980s report a high incidence (40% or greater) of major neurodevelopmental handicaps among survivors with birth weights from less than 800 grams. A resurgence of retrolental fibroplasia with severe visual impairment or blindness is reported in more than 10% of the very tiny infants weighing less than 1,000 grams. Because these infants account for less than 0.4% of all live births, however, they represent a very small total number. Mortality has been reduced in these fragile complicated infants but morbidity remains unacceptably high.

The present challenge is the development of perinatal and neonatal management techniques that result in far fewer physically, neurologically and developmentally handicapped children among those born weighing less than 1,001 grams.

ANNABEL J. TEBERG, MD
Los Angeles

Behrman RE: Preventing low birth weight: A pediatric perspective. J Pediatr 1985 Dec; 107:842-854

Hack M, Caron B, Rivers A, et al: The very low birth weight infant: The broader spectrum of morbidity during infancy and early childhood. J Dev Behav Pediatr 1983; 4:243-249

Teberg AJ, Wu PY, Hodgman JE, et al: Infants with birth weight under 1500 g: Physical, neurological and developmental outcome. Crit Care Med 1982 Jan; 10:10-14

Human Growth Hormone

DISTRIBUTION of the human growth hormone (hGH), obtained from the pituitary glands of cadavers, was suddenly discontinued in April 1985 following reports that three adults, ages 21 to 34, who received growth hormone treatment beginning in the 1960s had died of Creutzfeldt-Jakob disease, a slow virus infection of the brain. The disease was confirmed by pathologic examination of two patients; the other patient had clinical features of the disease but an autopsy was not done. Only growth hormone-deficient children with hypoglycemia were continued on treatment until a biosynthetic growth hormone was approved by the Food and Drug Administration in October 1985. Although current processing techniques are thought to destroy the virus, it is highly contagious and very resistant to chemical processing. Studies using animals are currently in progress to determine whether the virus can be transmitted in recent growth hormone preparations.

Contamination of hGH preparations with the Creutzfeldt-Jakob virus occurs in several ways: Human growth hormone was previously prepared from as many as 20,000 pituitary glands, yet patients with chronic neurologic diseases were not excluded from the donor population. Because the incubation period of Creutzfeldt-Jakob disease is long, some patients infected with the virus may have died before they were clinically symptomatic, and their infected pituitary glands were included in the donor pool. The incidence of the disease is one per million worldwide; in persons younger than 40, the incidence is .01 per million. Thus, the occurrence of three patients with Creutzfeldt-Jakob disease treated with hGH within one year strongly suggests that the infection was acquired from contaminated hGH preparations.

Although growth hormone-deficient children with hypoglycemia were continued on therapy, no treatment was available for many other growth hormone-deficient children until a biosynthetic human growth hormone (Protropin, Genentech Laboratories, South San Francisco, California) was approved in October 1985. Protropin, synthesized by recombinant DNA techniques using a strain of *Escherichia coli*, contains 191 amino acids identical to hGH plus methionone at the

N-terminal portion of the molecule. In clinical trials with Protropin in growth hormone-deficient children, linear growth rates were comparable to those in children receiving pituitary-derived hGH. Of 84 children treated with Protropin, antibodies to the growth hormone developed in 40%, but this did not interfere with growth except in one child.

The primary indication for treatment with synthetic human growth hormone is growth hormone deficiency shown by subnormal growth hormone response to two provocative tests. Some very short children growing less than 4.5 cm per year but with normal growth hormone levels in response to provocative stimulation have also responded to the use of human growth hormone, but indications for treatment are not well defined. The possible risks and benefits of treatment with hGH in other children with short stature is not yet known.

SUSAN J. CLARK, MD
Loma Linda, California

Brown P, Gajdusek DC, Gibbs CJ Jr, et al: Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N Engl J Med 1985 Sep; 313:728-731

Committee on Growth Hormone Use of the Lawson Wilkins Pediatric Endocrine Society: Degenerative neurologic disease in patients formerly treated with human growth hormone. J Pediatr 1985 Jul; 107:10-12

Gibbs CJ Jr, Joy A, Heffner R, et al: Clinical and pathological features and laboratory confirmation of Creutzfeldt-Jakob disease in a recipient of pituitary-derived human growth hormone. N Engl J Med 1985 Sep; 313:734-738

Koch TK, Berg BO, De Armond SJ, et al: Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism: Possible relation to the administration of cadaveric human growth hormone. N Engl J Med 1985 Sep; 313:731-733

Current Therapy for Asthma—New Inhalants

INHALATION THERAPY has increased in importance for the treatment of asthma as more effective drugs have become available and newer methods and techniques of delivery have been developed.

Several new β-adrenergic bronchodilator aerosol drugs are available for the treatment of asthma. One of the first β_2-agonists developed for asthma was isoproterenol, which has a short duration of activity and both β_1- and β_2-specific effects. In a search for more selective and longer acting drugs, new agents have been developed by modifying the chemical structure of the basic catecholamine molecule. Isoetharine has a duration of activity similar to that of isoproterenol, but is more β_2-selective. Noncatecholamine inhalants were subsequently developed and include metaproterenol, albuterol, terbutaline and bitolterol. These agents have a somewhat slower onset of action but a much longer duration of activity and greater β_2-selectivity than isoproterenol. Terbutaline, albuterol and bitolterol may be somewhat more bronchoselective and have a longer duration of activity than metaproterenol.

Although the new β-agonists are safer than their predecessors, they can cause adverse effects. Adverse cardiac effects can also be intensified by the concomitant use of theophylline, which can stimulate endogenous catecholamine release. Large doses of inhaled adrenergic agents alone or with theophylline can lead to hypopotassemia, thus greatly increasing the chance of cardiac arrhythmias. Paradoxical increases in airway obstruction and aggravation of hypoxemia reported following isoproterenol sulfate inhalations has not been reported with the newer, more selective agents. Sulfites, used as antioxidants, are present in bronchodilator solutions and have recently been found to cause bronchoconstriction in some susceptible patients with asthma. These substances, however, are not present in metered-dose inhalers or in the individual-dose vials of metaproterenol sulfate solution. With respect to tachyphylaxis, it is felt that the more selective β-agonists can be used for prolonged periods of time without fear of reducing bronchodilator activity.

One third to one half of patients use an improper technique when using metered-dose inhalers, and about 14% to 16% are unable to learn even after careful instruction. A new technologic development uses a spacer attachment consisting of a tube, cone or holding chamber between the actuator of the metered-dose inhaler and the patient's mouth. These devices not only improve delivery of the medication to the lungs and decrease oropharyngeal deposition but, of greatest importance, overcome the need for synchronization between firing the aerosol and inhaling. Large-volume spacers or reservoirs (500 to 1,500 cm) equipped with valves are particularly valuable in this respect. Several types are now available in this country, including Inhal-Aid, InspirEase, Breathancer and Aerochamber. Spacers may be of particular value for administering inhaled corticosteroids by reducing the incidence of oral candidiasis or dysphonia. Beclomethasone, triamcinolone and flunisolide are corticosteroids that can be prescribed for use as aerosols by metered-dose inhaler, as can cromolyn sodium (Intal Spinhaler); the triamcinolone inhaler is available with an attached spacer.

WARREN RICHARDS, MD
Los Angeles

American Academy of Allergy and Immunology Committee on Drugs: Position statement: Adverse effects and complications of treatment with β-adrenergic agonist drugs. J Allergy Clin Immunol 1985 Apr; 75:443-449

Konig P: Spacer devices used with metered-dose inhalers: Breakthrough or gimmick? Chest 1985; 88:276-284

McFadden ER Jr: Clinical use of β-adrenergic agonists. J Allergy Clin Immunol 1985 Aug; 76:352-356

Reed CE: β-Agonists—Adrenergic bronchodilators: Pharmacology and toxicology. J Allergy Clin Immunol 1985 Aug; 76:335-341

Oral Rehydration Therapy for Diarrhea

ORAL REHYDRATION THERAPY for diarrhea uses the principle of glucose-facilitated intestinal absorption of sodium and water to rapidly return a child to a euhydrated state. When successful, rehydration can be accomplished in 6 to 12 hours, obviating the need for parenteral therapy. Recent interest in oral rehydration therapy developed because of the need to find an effective, safe and practical treatment of dehydration associated with cholera in areas where parenteral therapy was unavailable. Use of the World Health Organization (WHO) oral rehydrating solution resulted in a dramatic decrease in mortality. Global acceptance of oral rehydration therapy is slowly evolving. Children have a prodigious capacity to absorb sodium-containing fluid at rates exceeding 15 ml per kg per hour. Intestinal sodium absorption can be facilitated in the presence of 2.0% to 2.5% glucose, but the glucose-linked sodium transport system becomes saturated with glucose concentrations greater than 3%, which may result in increased diarrhea due to intestinal hyperosmolarity. Fasting has a negative effect on sodium and water absorption.

Conventional therapy for diarrhea resulting in dehydration is to withhold oral fluids and replace deficits intravenously over 24 hours. Oral intake of fluids is usually reinstituted with small, frequent feedings of clear liquids followed by diluted formula. While effective and relatively safe, this regimen is empirical, expensive and disregards the capacity of the intestine to absorb fluid and electrolytes despite concomitant stool losses.